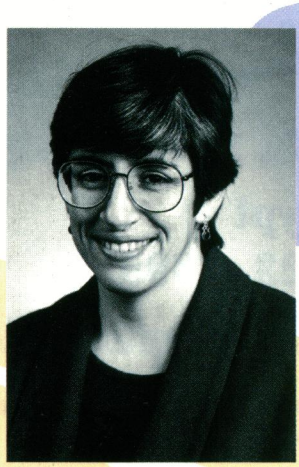
NIEHS News

Low-Level Estrogenic Effects



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Suzanne M. Snedeker

At the NIEHS-sponsored "Estrogens in the Environment II" conference held in Washington, DC, last winter, the issue of estrogenic chemicals in the environment and their possible adverse effects on reproduction was addressed. Estrogens are hormones that induce estrus and are responsible for the development and maintenance of female secondary sex characteristics. Chemical substances that exhibit biological activities similar to estrogens are considered estrogenic chemicals.

At the conference, researchers presented evidence of decreased reproductive capacity, feminization of male behavior, and feminization of male reproductive tissues in birds, fish, and reptiles. Reproductive failure has been reported in mammals, including seals and whales, that feed on contaminated fish and aquatic animals in polluted waterways. Many of the reproductive abnormalities observed in wildlife species have been associated with exposure to man-made chemicals, including organochlorine chemicals and pesticides, industrial waste products, and by-products of detergent surfactants, some of which have been shown to be weak estrogens. Many of the pesticides and chemicals associated with reproductive problems in animals and humans were banned from use in the United States during the 1970s and 1980s. However, there is still concern about exposures from chemicals that persist in the environment due to long half-lives and have the ability to bioaccumulate in fatty tissue and reach offspring transplacentally or through mother's milk.

Retrospective studies have reported a 50% decline in sperm counts in Western males and increased incidences of undescended testes, hypospadias, and an increased incidence of testicular cancer in certain Scandinavian countries. Increased incidences of fertility problems and breast cancer have also been reported. Although there is no known etiology to explain these health problems, it has been widely speculated that exposure to estrogenic chemicals in the environment may be responsible. There have been few attempts to estimate the level of environmental exposures to different estrogenic compounds, and no studies have examined the effect of administering mixtures of estrogenic chemicals on reproductive endpoints in mammals. Some of the chemicals identified as estrogenic may also have adverse effects on reproduction not due to their estrogenicity. However, increased incidence of a rare vaginal cancer in daughters of women who took the synthetic estrogen diethylstilbestrol (DES) during pregnancy, together with reports of an increased incidence of fertility problems in some DES daughters and increased incidence of male reproductive malformations in DES sons, suggest that reproductive tissues can be affected by *in utero* exposure to estrogens. It has not been substantiated that chronic, low-dose environmental exposures to estrogenic chemicals, *in utero* and through the reproductive years, cause reproductive abnormalities similar to those related to DES. Chemicals that are not estrogenic are also known to have adverse effects on reproduction by affecting endocrine pathways, which may influence the metabolism of female or male sex steroids.

To address these questions, Suzanne Snedeker and her colleagues in the Environmental Toxicology Program at the NIEHS are designing studies using the rat to determine if low-dose, chronic exposures to selected estrogenic chemicals and other chemicals known to disrupt endocrine pathways affect reproductive systems of mammals. These studies are anticipated to begin in 1994.

Levels of exposures will include low doses that are similar to levels of the chemicals found in the environment, as well as higher doses associated with occupational exposures. Chemicals will be administered singly as well as in mixtures to mimic environmental exposures. Exposures and assessments of reproduction will be carried out over multiple generations, and recovery from any observed effects will be assessed in succeeding, nonexposed generations. Because the incidence of certain cancers has been shown to be affected by *in utero* exposure to estrogens, and standard carcinogenicity bioassays do not cover *in utero* exposures, selected reproductive tract and endocrine tissues will be examined for preneoplastic and/or neoplastic changes. Reproductive changes will be assessed through measures of fertility, spermatogenesis in males and cyclicity in females, pup viability, and changes in serum testosterone, estrogen, progesterone, lutenizing hormone, and follicle-stimulating hormone. Tissue will be examined for changes, including histopathological changes, that indicate estrogenization of females, or feminization in males. For example, in males exposed to estrone *in utero*, the normal cuboidal epithelium in the coagulating gland and seminal vesicle becomes "feminized," forming a stratified squamous epithelium, similar to that found in the female vagina during estrus. In females, estrogens can cause the vagina to open early, and female rodents exposed to DES *in utero* have an increased incidence of abnormal coiling of the oviduct.

Because only a limited number of chemicals can be included in this study, selection of chemicals will be based on 1) evidence for estrogenicity or disruption of reproductive endocrine pathways, 2) evidence for transfer to offspring transplacentally or via breast milk, 3) current widespread use or persistence of the chemical or metabolites in the environment, 4) ability to enter the food chain via groundwater, sewage contaminants, as residues on food, or by accumulation in seafood, 5) evidence of occupational exposure in industrial or agricultural applications, and 6) potential for affecting reproductive or endocrine endpoints. These studies should provide a basis for determining if exposures to low levels of chemicals, which affect endocrine pathways, cause reproductive disorders in mammals including humans.

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Lynn R. Goldman

Goldman Elected Chair of NTP Executive Committee

Lynn Goldman, assistant administrator for the EPA's Office of Prevention, Pesticides, and Toxic Substances, has been elected chair of the Executive Committee of